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ORIGINAL RESEARCH

Differences in Clinical Characteristics of AECOPD Patients with or without *Candida* Isolation from the Lower Respiratory Tract

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Background: *Candida* species are frequently found in the lower respiratory tract (LRT) of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), but the clinical significance is uncertain. This study compared the clinical differences between AECOPD patients with and without *Candida* in their LRT and assessed the impact on disease outcomes.

Methods: We conducted a retrospective case-control study on AECOPD patients hospitalized at the First Affiliated Hospital of Guangxi Medical University. Demographic characteristics, clinical data, and follow-up data were compared between AECOPD patients with and without *Candida* isolated from their LRT. Univariate and multivariate logistic regression analyses were performed to identify risk factors for AECOPD. Survival curves for the patients with and without *Candida*-positive LRT samples were calculated using the Kaplan–Meier method.

Results: A total of 225 hospitalized AECOPD patients were included in the study, 88 of whom had *Candida* isolated from their LRT, while 137 did not. The *Candida*-positive group had a greater pack-year history and higher COPD Assessment Test (CAT) scores compared to the *Candida*-negative group. The proportion of patients with Modified Medical Research Council (mMRC) grade 4, Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) grade 4 and hospitalizations for AECOPD in the past year were higher in the *Candida*-positive group. Peripheral blood lymphocytes, $CD8^+$ T-lymphocytes and percent predicted forced expiratory volume in 1 s (FEV_1) were significantly lower in the *Candida*-positive group ($P < 0.05$). Patients without *Candida* survived significantly longer than those with *Candida* ($P < 0.001$). The presence of *Candida* and mMRC grade 4 were independent risk factors for both acute exacerbation and hospitalization in the past year.

Conclusion: Positive C*andida* isolation and mMRC grade 4 are independent risk factors for AECOPD. *Candida* in the LRT of COPD patients may predict more severe clinical symptoms, greater airflow limitation, and poorer survival outcomes.

Keywords: chronic obstructive pulmonary disease, *Candida*, the lower respiratory tract, risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway disease characterized by persistent airflow limitation. Acute exacerbation (AE) has always been regarded as a key indicator of COPD in clinical research. Bacteria and viruses are the most common infectious factors that induce AE, and bacterial colonization is an important cause of acute exacerbations of COPD (AECOPD), which is often overlooked.[1] In recent years, the effect of fungi derived from the lower respiratory tract (LRT) on COPD has attracted the attention of researchers. Studies have shown that abundant fungal biota exists in the induced sputum of COPD patients, with *Aspergillus* and *Penicillium* being associated with frequent AEs and high

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mortality.[2–4] Although the isolation rate of *Candida* from the LRT is much higher than that of other pathogenic fungi, it is often considered as contamination or simple colonization of *Candida* in the airway without clinical significance.[5,6] Therefore, there are few studies on the influence of positive *Candida* isolation from the LRT on COPD.

Candida is one of the most common opportunistic pathogenic fungi found in humans. It often exists on the surface of the LRT mucosa in the form of yeast; however, with changes in the environment, it can shift from a symbiotic to a pathogenic state. It can cause infection when mucosal or skin barrier function is disrupted, the number and function of neutrophils are impaired, cellular immunity is compromised, and metabolic dysfunction occurs. When the immune system functions properly, *Candida* typically coexists peacefully with the host as a colonizer, in contrast to yeast, mycelia have a stronger ability to invade and damage host cells.[7–9] At present, it is not clear whether the long-term presence of *Candida* in the LRT of COPD patients serves as a marker that potentially leads to AEs or affects disease severity. However, many studies have demonstrated that airway *Candida* colonization is associated with poor efficacy and prognosis in patients in intensive care units (ICUs).[10,11]

A retrospective study of 16 hospitals in China over a 10-year period found that *Candida* pneumonia accounted for 11.4% of all fungal pneumonia cases, with COPD being the second most common comorbidity.[12] Generally, invasive candidiasis is secondary to colonization, and mucosal colonization is considered an independent risk factor for invasive candidiasis.[13] Most patients experience varying durations and degrees of colonization before the onset of *Candida* infection, and multisite colonization is associated with a higher risk of *Candida* infections.[13] It is believed that pathogen colonization in the LRT is an important factor in the pathogenesis of ventilator-associated pneumonia, and reducing bacterial colonization in the LRT is also an important prevention strategy for ventilator-associated pneumonia. *Candida* colonization serves as a precursor risk factor for *Candida* infection, which may be a risk factor and a predictive indicator for *Candida* infection in deep organs.[14–16]

To further investigate the impact of positive *Candida* isolation in the LRT on AECOPD patients, we conducted a retrospective case-control study. This study compared the clinical characteristics of AECOPD patients with and without *Candida* isolation in the LRT and assessed the influence of *Candida* presence on AE events and long-term prognosis.

Materials and Methods

Study Design and Patient Population

This is a retrospective case-control study involving AECOPD patients hospitalized at the First Affiliated Hospital of Guangxi Medical University from January 1, 2018, to December 31, 2020. All patients or their immediate family members provided written informed consent. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (no. 2022-KY-E-144, 2025-E1032). This study adheres to the Declaration of Helsinki.

The inclusion criteria were as follows: (1) Fulfillment of the COPD diagnostic criteria of the 2019 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD): patients exhibited symptoms such as recurrent cough, sputum production, shortness of breath, and pulmonary function tests indicating a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70% after inhalation of a bronchodilator, leading to a diagnosis of COPD. (2) Fulfillment of the diagnostic criteria for AE, including shortness of breath, cough, and/or sputum production with acute changes beyond normal daily variations and necessitating hospitalization.

The exclusion criteria were as follows: (1) age < 50 years; (2) hospitalization due to other systemic diseases; (3) no sputum production during hospitalization; (4) presence of oral candidiasis or oral leukoplakia; (5) isolation of fungi other than *Candida* from the LRT; (6) isolation of *Candida* from other specimens (such as blood, stool, or urine); (7) failure to obtain induced sputum or bronchoalveolar lavage fluid (BALF).

Population Groupings

In our study, LRT samples consist of induced sputum or BALF. According to the results of pathogenic detection in LRT samples from AECOPD patients during hospitalization, patients with at least one smear or culture positive for *Candida* were classified into the *Candida*-positive group; otherwise, they were classified into the *Candida*-negative group.

Data Collection and Follow-up

The data collected included demographic characteristics (e.g., age, sex, body mass index, duration of COPD, smoking status, COPD severity grading, complications and comorbidities) and clinical data (such as the frequency of AEs in the past year and laboratory examination results). Patients underwent follow-up assessments every 3 to 6 months. The follow-up period concluded on April 30, 2022, at which point the patients' survival status was documented. The primary outcome of this study was AE events and the secondary outcome was death events.

Statistical Analysis

All data were statistically analyzed using SPSS 25 (IBM, Armonk, NY). For variables that were normally distributed, data were presented as mean ± standard deviation (SD), and comparisons between the *Candida*-positive and *Candida*-negative groups were performed using the independent sample *t*-test. For variables that did not follow a normal distribution, data were expressed as median with interquartile range (IQR), and between-group comparisons were conducted using the Mann–Whitney U- test. Categorical variables were expressed as percentages, and comparisons between groups were performed using the chi-squared test. The Kaplan-Meier method was used to generate survival curves for the two groups, and the Log rank test was used to compare survival rates between groups. Statistical significance was set at $P < 0.05$. Risk factors for AECOPD were identified using binary logistic regression analysis on the variables with statistically significant differences.

Results

Pathogen Isolation in the LRT

A flowchart illustrating the process is presented in Figure 1. Two hundred and twenty-five patients were enrolled in this study. According to the results of pathogen isolation from the LRT, the patients were divided into two groups: a *Candida*-

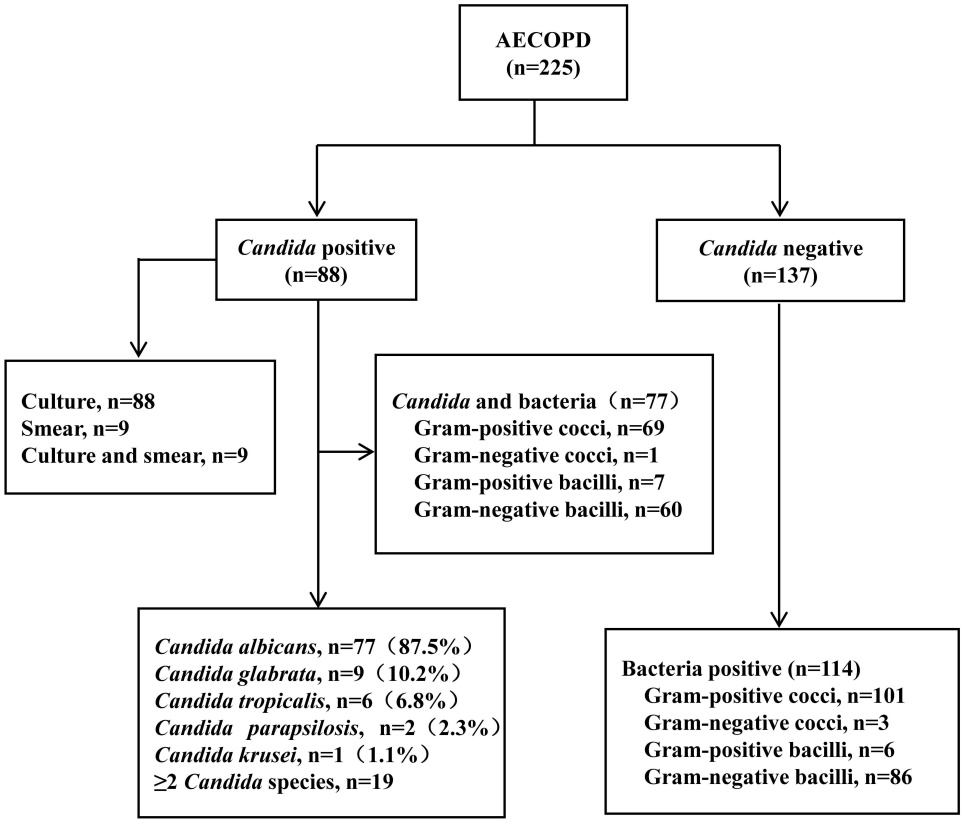

Figure 1 *Candida* detection chart of study population. AECOPD, acute exacerbation of chronic obstructive pulmonary disease. *Candida glabrata* has now been reclassified as *Nakaseomyces glabrata*, and *Candida krusei* as *Pichia kudriavzevii*.

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positive group (n = 88) and a *Candida*-negative group (n = 137). The detected species included *C. albicans* (87.5%), *C. glabrata* (now called *Nakaseomyces glabratus*,[17] 10.2%), *C. tropicalis* (6.8%), *C. parapsilosis* (2.3%), and *C. krusei* (now called *Pichia kudriavzevii*,[17] 1.1%). Among patients in the Candida-positive group, 77 had bacterial isolates, including 69 cases of Gram-positive cocci, 1 case of Gram-negative cocci, 7 cases of Gram-positive bacilli, and 60 cases of Gram-negative bacilli. In the Candida-negative group, 114 had bacterial isolates, including 101 cases of Gram-positive cocci, 3 cases of Gram-negative cocci, 6 cases of Gram-positive bacilli, and 86 cases of Gram-negative bacilli. Although bacteria were detected in the LRT secretion smears of most patients, there was no significant difference in the positive rate of bacteria between the two groups (87.5% vs. 83.2%, $P > 0.05$). This suggests that the baseline characteristics of the two groups were comparable, including the positive detection rate of sputum microbial etiology. Viral testing for pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza was negative in all included patients.

Baseline Characteristics of Hospitalized AECOPD Patients

The mean age of the *Candida*-negative group was 69.18 ± 9.48 years, including 124 males and 13 females, and the mean age of the *Candida*-positive group was 71.40 ± 9.43 years, including 77 males and 11 females. There were no significant differences in sex, age, disease duration, body mass index, or complications between the two groups ($P > 0.05$). One hundred and ninety-five (86.7%) patients had a history of heavy smoking for a prolonged period, but the smoking index of the *Candida*-positive group was higher (54.35 ± 29.68 vs. 45.89 ± 28.93, $P < 0.05$). Furthermore, the *Candida*-positive group exhibited more severe symptoms, with higher COPD Assessment Test (CAT) scores and a higher proportion of patients with a modified Medical Research Council (mMRC) score of 4 and GOLD score of 4 ($P < 0.05$).

The percentage of FEV_1% (FEV_1% predicted, 41.94 ± 19.60 vs. 50.62 ± 22.88, $P < 0.05$) and the absolute FEV_1 values [1.18 (0.62, 1.61) L vs. 1.33 (0.73, 1.43) L, $P < 0.05$] in the *Candida*-positive group were significantly lower than those in the *Candida*-negative group. These findings suggest that *Candida* colonization may exacerbate pulmonary function impairment in COPD patients. We evaluated AEs in patients and found that more than half of the patients in both groups had experienced AEs in the past year, although this difference was not statistically significant. Notably, the proportion of patients in the *Candida*-positive group who required hospitalization following an AE (51/60, 85.0%) was higher than that in the *Candida*-negative group (51/82, 62.2%), suggesting that AEs were more severe in the *Candida*-positive group. Detailed data are presented in Table 1.

Laboratory Examination Results

An analysis of the initial routine blood examinations in the two groups, including white blood cell count (WBC), absolute value of neutrophils (NE), absolute value of eosinophils (EOS), and absolute value of lymphocytes (LYM), revealed that the LYM count in the *Candida*-positive group was significantly lower than that in the *Candida*-negative group ($P < 0.05$). Additionally, the peripheral blood $CD8^+$ T-lymphocyte count in the *Candida*-positive group was lower (292.80 ± 185.70 cells/μL vs. 380.00 ± 236.10 cells/μL, $P < 0.05$). Although a similar trend was observed in the comparison of $CD4^+$ T-lymphocyte counts between the two groups, the difference was not statistically significant. The data are presented in Table 2.

Survival Analysis

Patients in both groups were followed up every 3 to 6 months. In the *Candida*-negative group, 19 patients (13.87%) died, and the survival rates at 12, 24, and 36 months were 93.4% (95% CI 89.28% - 97.52%), 91.0% (95% CI 86.1% - 95.9%), and 84.5% (95% CI 78.03% - 90.97%), respectively. Conversely, in the *Candida*-positive group, 33 patients (37.5%) died, and the corresponding survival rates at 12, 24, and 36 months were 80.7% (95% CI 72.47% - 88.93%), 70.1% (95% CI 60.49% −79.7%), and 59.1% (95% CI 47.93% - 70.27%), respectively. The survival rate in the *Candida*-positive group was significantly lower than that in the *Candida*-negative group ($P < 0.001$, HR 3.257, 95% CI 1.850–5.735; Figure 2).

Table 1 Baseline Characteristics of Hospitalized AECOPD Patients with or without *Candida* Isolation

Variables	*Candida* Negative (n=137)	*Candida* Positive (n=88)	*P* value
Age, year	69.18±9.48	71.40±9.43	0.211
Male (Female), n	124 (13)	77 (11)	0.511
Body mass index, kg/m^2	21.52±3.78	20.55±3.52	0.083
Duration of COPD, year	9.06±8.60	11.60±10.19	0.149
Duration of inpatient stay, days	9.96±5.420	11.49±7.61	0.119
Smoking status, n (%)	121 (88.3)	74 (84.1)	0.422
Pack-year history	45.89±28.93	54.35±29.68	0.019*
CAT, score	18.38±3.41	20.02±3.20	0.0004***
mMRC, score, n (%)			
1	15 (11.0)	1 (1.1)	0.006**
2	46 (33.6)	24 (27.3)	0.337
3	53 (38.6)	35 (39.8)	0.889
4	23 (16.8)	28 (31.8)	0.014*
GOLD, classification, n (%)			
1	10 (9.8)[a]	2 (3.8)[b]	0.339
2	28 (27.5)[a]	15 (28.8)[b]	0.851
3	49 (48.0)[a]	19 (36.5)[b]	0.229
4	15 (14.7)[a]	16 (30.8)[b]	0.032*
FEV_1% pred	50.62±22.88	41.94±19.60	0.026*
FEV_1, L	1.33 (0.73, 1.43)	1.18 (0.62, 1.61)	0.005**
FEV_1/FVC (%)	50.29±42.77	43.61±12.87	0.291
Patients had AE events in the past year, n (%)	82 (59.9)	60 (68.2)	0.257
Hospitalized AECOPD in the past year, n (%)	51 (62.2)[c]	51 (85.0)[d]	0.003**
Systemic glucocorticoid therapy within 180 days, n (%)	29 (21.2)	16 (18.2)	0.585
Antibiotic therapy within 180 days, n (%)	77 (56.2)	44 (50.0)	0.362
Respiratory failure, n (%)	33 (24.1)	32 (36.4)	0.0516
Pulmonary heart disease, n (%)	41 (29.9)	31 (35.2)	0.4645
Pulmonary encephalopathy, n (%)	5 (3.7)	2 (2.3)	0.7076
Bronchiectasis, n (%)	8 (5.8)	12 (13.6)	0.057
Pneumonia, n (%)	34 (24.8)	24 (27.3)	0.755
Malignant tumor, n (%)	6 (4.4)	6 (6.8)	0.545
Hypertension, n (%)	46 (33.6)	32 (36.4)	0.669
Coronary heart disease, n (%)	6 (4.4)	10 (11.4)	0.062
Diabetes, n (%)	13 (9.5)	15 (17.1)	0.102
Gout, n (%)	5 (3.7)	3 (3.4)	1.000

Notes: [a]n=102, [b]n=52, [c]n=82, [d]n=60; Data are expressed as numbers, percentages, mean ± standard deviation, or median with interquartile range. $P<0.05$ is statistically significant (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

Abbreviations: AE, acute exacerbation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAT, COPD Assessment Test; mMRC, modified Medical Research Council; GOLD, Global Initiative for Chronic Obstructive Lung Disease; $FEV_{1\%}$ pred, forced expiratory volume in 1 s (% of predicted); FEV_1, forced expiratory volume in 1 s.

Positive Candida Isolation in the LRT and mMRC-4 as Independent Risk Factors for AEs and Hospitalization in COPD Patients in the Past year

AE has consistently been recognized as a key indicator of COPD in clinical research. Logistic regression analysis identified the presence of *Candida* in the LRT and mMRC 4 as independent risk factors for AE events in the past year [odds ratio (OR) = 1.949, $P = 0.036$; OR = 2.893, $P = 0.012$] and for COPD patients with AEs requiring hospitalization in the past year (OR = 1.931, $P = 0.022$; OR = 2.977, $P = 0.001$). These findings indicate that the positive *Candida* isolation in the LRT is not only associated with AEs but also serves as a risk factor for both AEs and hospitalization. The relevant data are shown in Table 3 and Table 4.

Table 2 Laboratory Examination Results in Hospitalized AECOPD Patients with or without *Candida* Isolation

Laboratory Examination	*Candida* Negative (n=137)	*Candida* Positive (n=88)	*P* value
White blood cell (10^9/L)	9.15±4.63	8.62±3.07	0.653
Neutrophils (10^9/L)	6.68±4.41	6.40±3.05	0.312
Eosinophil (10^9/L)	0.22±0.34	0.24±0.49	0.142
Lymphocyte (10^9/L)	1.49±0.84	1.25±0.67	0.033*
$CD4^+$ T cells (cells/μL)	530.00±333.10[a]	396.00±218.50[b]	0.075
$CD8^+$ T cells (cells/μL)	380.00±236.10[a]	292.80±185.70[b]	0.045*
C-reactive protein (>10 mg/L), n (%)	61 (44.53)	48 (54.55)	0.182
ESR (>20 mm/H), n (%)	58 (58.00)[c]	45 (61.64)[d]	0.642
Procalcitonin (ng/mL)	0.08 (0.04, 1.66)[e]	0.05 (0.02, 0.10)[f]	0.372
Immunoglobulin E (g/L)	34.92 (16.41, 97.22)[g]	103.06 (15.04, 208.75)[h]	0.109
Serum galactomannan (pg/mL)	0.22 (0.14, 0.30)[i]	0.32 (0.16, 0.43)[j]	0.642
Serum (1, 3)- β- D-glucan (>20 pg/mL), n (%)	17 (13.71)[k]	4(4.94)[l]	0.074
Blood gas analysis	7.41±0.07	7.39±0.07	0.116
PO_2 (mmHg)	73.83±20.53	77.77±31.81	0.867
PCO_2 (mmHg)	50.07±17.25	52.79±15.07	0.079

Notes: [a]n=53, [b]n=41, [c]n=100, [d]n=73, [e]n=106, [f]n=68, [g]n=46, [h]n=29, [i]n=125, [j]n=82, [k]n=124,[l]n=81; Data are expressed as numbers, percentages, mean ± standard deviation, or median with interquartile range. *P<0.05 is statistically significant.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; PO_2, arterial partial pressure of oxygen; PCO_2, arterial partial pressure of carbon dioxide.

Discussion

Previous clinical studies have demonstrated that more than half of hospitalized AECOPD patients were positive for *Candida* isolates from the LRT.[6,18] In the present study, 88 cases (39.1%) exhibited *Candida* presence in LRT specimens, with *C. albicans* accounting for the majority at 87.5%, a proportion significantly higher than that of other *Candida* species. The

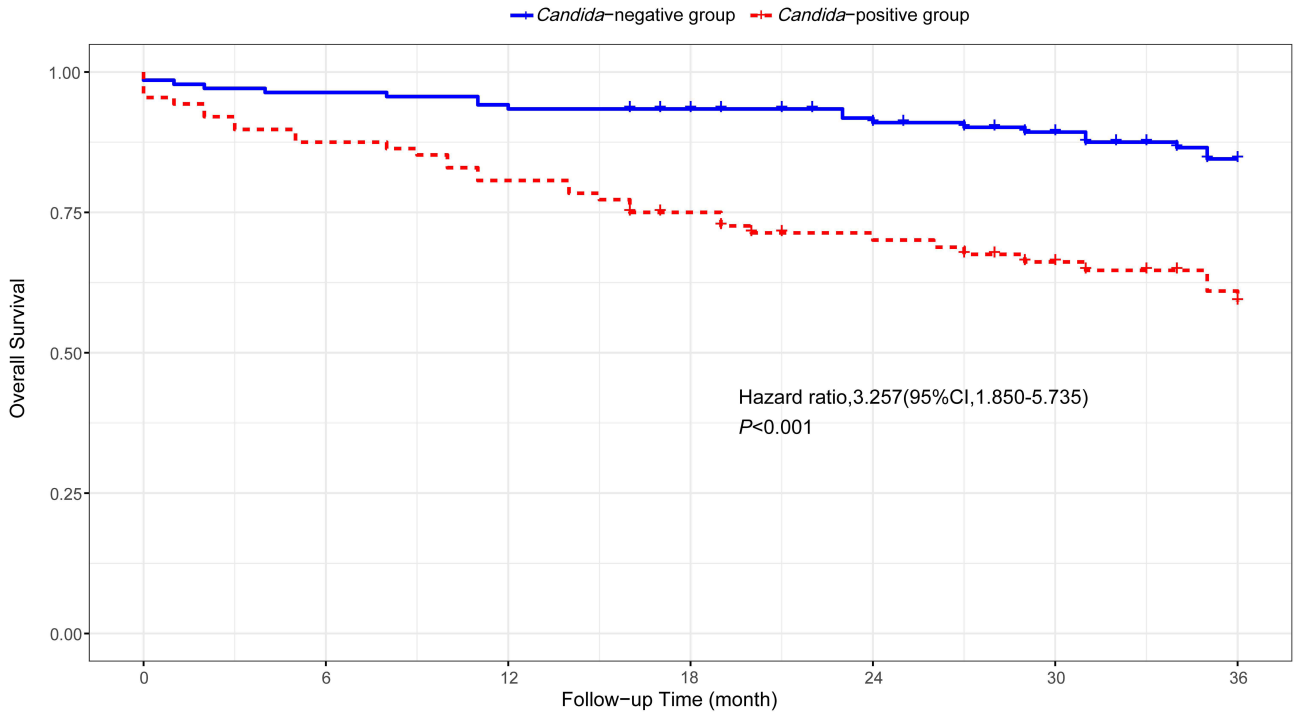

Figure 2 Survival curve of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease with or without *Candida* isolation.

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Table 3 Univariable Logistic Regression Analysis of Predictors for AE Events and Hospitalized AECOPD in the Past year

Variables	AE Events in the Past Year			Hospitalized AECOPD in the Past Year		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Candida (+)	2.280	(1.246, 4.173)	0.008**	2.219	(1.285, 3.830)	0.004**
CAT	1.124	(1.036, 1.220)	0.005**	1.132	(1.049, 1.222)	0.001**
mMRC 4	3.476	(1.542, 7.839)	0.003**	3.338	(1.733, 6.430)	0.000***
GOLD 4	1.200	(0.526, 2.740)	0.665	1.506	(0.684, 3.314)	0.309
Age, year	0.996	(0.968, 1.024)	0.768	1.006	(0.979, 1.033)	0.665
Duration of COPD, year	1.000	(0.971, 1.030)	1.000	0.993	(0.965, 1.022)	0.634
Lymphocytes (10^9/L)	1.013	(0.712, 1.441)	0.994	0.901	(0.643, 1.263)	0.547
Pack-year history	1.010	(1.000, 1.019)	0.040*	1.004	(0.996, 1.012)	0.342
FEV_1%pred	0.987	(0.970, 1.003)	0.114	0.989	(0.972, 1.007)	0.222
FEV_1 (L)	1.118	(0.615, 2.032)	0.714	1.029	(0.581, 1.822)	0.923

Notes: *P*<0.05 is statistically significant (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).
Abbreviations: AE, acute exacerbation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV_1% pred, percent predicted forced expiratory volume in 1 s; mMRC, modified Medical Research Council; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 4 Multivariate Logistic Regression for Predictors of AE Events and Hospitalized AECOPD in the Past year

Variables	AE Events in the Past Year			Hospitalized AECOPD in the Past Year		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Candida (+)	1.949	(1.045, 3.635)	0.036*	1.931	(1.099, 3.394)	0.022*
CAT	1.029	(0.918, 1.153)	0.624	1.017	(0.913, 1.133)	0.759
mMRC 4	2.893	(1.261, 6.637)	0.012*	2.977	(1.527, 5.805)	0.001**
Pack-year history	1.008	(0.998, 1.018)	0.104	1.002	(0.993, 1.010)	0.677

Notes: *P*<0.05 is statistically significant (*$P < 0.05$, **$P < 0.01$).
Abbreviations: AE, acute exacerbation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAT, COPD Assessment Test; mMRC, modified Medical Research Council.

symptoms in the *Candida*-positive group were more severe than those in the *Candida*-negative group, and the CAT score and mMRC-4 grade ratio in the former were significantly higher than those in the latter. These findings are consistent with previous multicenter, large-sample case-control studies.[18]

The results also showed that airflow limitation was more severe in the *Candida*-positive group, as evidenced by a lower FEV_1% predicted level and a higher proportion of patients classified as GOLD-4 grade. Furthermore, follow-up data revealed that the survival rate in the *Candida*-positive group was significantly lower than that in the *Candida*-negative group. Consequently, the presence of *Candida* in the airway may be associated with exacerbation of symptoms, increased disease severity, and poor prognosis in patients with COPD. The anatomical characteristics of the LRT are different from those of the skin and mucous membranes. Colonization of the airway mucosa by *Candida* can lead to increased secretion and bronchial obstruction, resulting in the corresponding clinical manifestations or aggravation of the existing symptoms. Furthermore, *C. albicans* is a prevalent fungus responsible for allergic bronchopulmonary mycosis in addition to *Aspergillus*, and can cause allergic reactions or asthma-like symptoms in COPD.[19,20]

AE constitute a critical event in the progression of COPD. We observed a significant trend of hospitalization after AEs in the *Candida*-positive group over the past year. Further analysis identified positive *Candida* isolation and mMRC-4 grades as two important independent risk factors for AEs and severe conditions requiring hospitalization after AEs in the past year. In addition to the previously mentioned factors contributing to aggravating symptoms and airflow limitation, interactions among mixed pathogens in the airway are also major causes that cannot be ignored. Although the role of *Candida* colonization in the progression of bacterial pneumonia remains controversial, the prevalence of mixed colonization or infection is notably high

among patients with COPD. Our research showed a significant prevalence of concurrent detection of *Candida* and other bacterial pathogens in these patients. *Candida*, bacteria, and other pathogens exist in the airway for long period can influence each other through direct contact or indirect regulation, including enhanced physical contact or adhesion, mixed biofilm formation, the effects of quorum sensing molecules or metabolites, changes in virulence, alterations to the microenvironment, affecting host immunity, and even modification of disease outcomes.[21–24] For example, *Staphylococcus aureus* demonstrates significantly increased antimicrobial tolerance when exposed to exogenously supplemented farnesol or farnesol secreted by *C. albicans* in biofilms.[25] Moreover, *C. albicans* can augment the secretion of α and δ toxins by enhancing the accessory gene regulator quorum-sensing system of *S. aureus*, resulting in synergistic lethality during pathogen co-infection (whereas single microbial infection is not fatal).[26] Lactic acid produced by bacteria can inhibit the transition of *C. albicans* from yeast to mycelium and mask the key pathogen-related molecular pattern (β-glucan) on the surface of *C. albicans* cells, both of which are strategies to evade host immune detection.[27,28] Such interactions may contribute to the frequent AEs and disease progression in patients with airway *Candida* colonization. In our study, there were no significant differences between the two groups in either the isolation rate or the distribution of bacterial types, suggesting that bacterial co-detection was unlikely to be a major factor contributing to the differences in clinical outcomes between the two groups.

The use of antifungal drugs to eliminate *Candida* from airway colonization remains controversial, as the benefits of antifungal therapy for patients, including critically ill individuals, remain unclear.[29–31] Nonetheless, a previous study has demonstrated a significantly reduction in the incidence of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa* after antifungal therapy in patients with airway *C. albicans* colonization.[32] Furthermore, animal studies have shown that airway colonization by *Candida* in rats is associated with a marked increase in the incidence of bacterial pneumonia, which subsequently decreases following intervention with fluconazole or amphotericin B.[33,34] In COPD patients who have been using inhaled corticosteroids for a long time, *C. albicans* isolated from LRT specimens does not provide a definitive distinction between colonization and infection due to the absence of pathological evidence. Consequently, it remains unclear whether the elimination of *Candida* from the airway contributes to a reduction in the frequency of AEs, alleviating disease symptoms, or delaying the progression of COPD. This issue requires closer monitoring, comprehensive evaluation, and individualized assessment to determine the necessity of antifungal treatment.

The decline or disorder of immune function in COPD can impair respiratory defense mechanisms, which may lead to the colonization or infection by pathogens and accelerate disease progression. Studies have shown that the counts of $CD4^+$ and $CD8^+$ T-cells in the peripheral blood of AECOPD patients are lower than those in the stable phase.[35] In this study, we observed that the $CD8^+$ T cell count in the *Candida*-positive group was significantly lower than that in the *Candida*-negative group, with a similar trend observed for $CD4^+$ T-cell counts between the two groups. This observation raises the question of whether the presence of *Candida* in the airway exacerbates the degree of impaired cellular immunity, immune imbalance, or inflammatory responses. Interestingly, antifungal therapy in patients with hospital-acquired bacterial pneumonia who also exhibit *Candida* airway colonization showed decreased levels of inflammatory markers (IL-6, tumor necrosis factor-α, and interferon-γ) and an increased number of $CD4^+$ T lymphocytes. This observation suggests that airway colonization by *C. albicans* may affect the immune response in COPD patients, which requires further investigation.[36]

This study had several limitations. First, it was a retrospective study based on electronic medical records and was conducted at a single center, and subjective bias could not be completely avoided during the research process. Second, retrospective studies are limited in their ability to establish causality and control for confounding factors, which need to be further addressed by prospective studies. Finally, the study classified participants into different groups based on the results of *Candida* smear or culture of LRT specimens (mainly sputum); however, it was unable to clearly differentiate between colonization and infection, as pathological evidence was lacking.

Despite its limitations, this study reaches a convincing conclusion that airway *Candida* colonization should no longer be viewed as a simple bystander in COPD and may affect the degree of airflow limitation, the risk of AE, and long-term prognosis. Attention should be given to whether antifungal treatment could benefit AECOPD patients with *Candida* airway colonization.

Conclusions

Candida spp. were detected in the LRT secretions of more than one-third of hospitalized AECOPD patients. *Candida* isolation and an mMRC grade of 4 are independent risk factors for AECOPD. *Candida* colonization of the LRT may predict more severe clinical symptoms, greater airflow limitation, and a poorer prognosis in patients with AECOPD.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author (Jianquan Zhang, zhangjq76@mail.sysu.edu.cn) on reasonable request.

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Disclosure

Xuan Wei, Xiaofeng Li and Jiehua Deng contributed equally to this work and should be considered co-first authors. The authors declare that they have no competing interests.

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